AD_____

Award Number: W81XWH-11-1-0738

TITLE: Family Studies of Sensorimotor and Neurocognitive Heterogeneity in Autism Spectrum Disorders (ASD)

PRINCIPAL INVESTIGATOR: John Sweeney, Ph.D.

CONTRACTING ORGANIZATION: University of Texas Southwestern Medical Center

Dallas, Texas 75390-9086

REPORT DATE: September 2013

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
September 2013	Annual	1 September 2012 – 31 August 2013

4. TITLE AND SUBTITLE
Family Studies of Sensorimotor and Neurocognitive Heterogeneity in Autism Spectrum Disorders (ASD)

5a. CONTRACT NUMBER
W81XWH-11-1-0738

5b. GRANT NUMBER
W81XWH-11-1-0738

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
John A. Sweeney, Ph.D.; Matthew W. Mosconi, Ph.D.

E-Mail: john.sweeney@utsouthwestern.edu; matt.mosconi@utsouthwestern.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas Southwestern Medical Center
Center for Autism and Developmental Disabilities
5323 Harry Hinds Boulevard, MC9086
Dallas, Texas 75390-9086

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Autism spectrum disorders (ASD) are complex heritable neurodevelopmental disorders. It is likely that these disorders include individuals with different familial etiopathological mechanisms, and thus identifying biologically homogeneous subgroups of affected individuals and families is an important step to speed identification of risk genes and the development of more individualized and effective treatments. Using eye movement testing, we previously identified a profile of neurophysiological alterations in unaffected parents and siblings of individuals with ASD that was strikingly similar to that reported in ASD patients by our group and others. These data implicated ponto-cerebellar circuitry, left hemisphere frontotemporal circuitry, and prefrontal systems that were relatively independently affected. The proposed study aims to examine these promising biological intermediate phenotypes by evaluating eye and hand movement neurophysiology in family trios consisting of an individual with ASD and their unaffected biological parents. Consistent with our target recruitment rates, we have studied 30 family trios and 46 healthy controls to date including 19 family trios and 39 healthy controls during the past year. We will begin initial analyses of probands and family data during the upcoming last year of the award.

15. SUBJECT TERMS
Autism, family study, sensorimotor, neurocognitive

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU		

Table of Contents

INTRODUCTION

Autism spectrum disorders (ASD) are complex heritable neurodevelopmental disorders. It is likely that these disorders include individuals with different familial etiopathological mechanisms, and thus identifying biologically homogeneous subgroups of affected individuals and families is an important step to speed identification of risk genes and the development of more individualized and effective treatments. Using eye movement testing, we previously identified a profile of neurophysiological alterations in unaffected parents and siblings of individuals with ASD that was strikingly similar to that reported in ASD patients by our group and others. These data implicated ponto-cerebellar circuitry, left hemisphere frontotemporal circuitry, and prefrontal systems that were relatively independently affected. The proposed study aims to examine these promising biological intermediate phenotypes by evaluating eye and hand movement neurophysiology in family trios consisting of an individual with ASD and their unaffected biological parents. This combined use of oculomotor and manual motor tasks will not only enhance our search for and understanding of familial phenotypes in ASD, but importantly it will provide a fuller characterization of sensorimotor deficits in these disorders.

II: BODY

a. Overall Progress. We have successfully completed each of the tasks laid out in our original Statement of Work for Year 2. During the past year, we have met our goals for recruiting family trios and healthy controls. Each subject has completed neurocognitive and sensorimotor testing. We also have continued regular quality assurance testing to check the integrity of test administration, data processing, data analysis and data entry. A brief synopsis of our progress in each of these areas is provided below.

IRB: No major modifications have been made to our current IRB. We have made the following minor modifications during the past year:

Modification – Approved 10/18/2012 –

1. Removed Subhash Aryal, Ph.D. and Marilynn Sweeney from the study, and added Preston Wiles, M.D., Mary Ann Morris, Ed.D., Patricia Evans, M.D., Stormi White, Psy.D., and Cristin Dooley, Ph.D. as “Study Doctors”.
2. HIPPA authorization and consent forms were updated to include time of consent according to newly revised standards of the UT Southwestern IRB.
3. The primary research coordinator was changed from Lauren Schmitt to Rachel Greene.
4. We transitioned from using the WPPSI-III to using the new WPPSI-IV.
5. The protocol was modified in the following ways:
   a. The following tests were discontinued to reduce subject burden: Social Responsiveness Scale (SRS), Edinburgh Handedness Test, Dot Locations and Word Pairs subtest from the Children’s Memory Scale, Trails B, Digit Span and Spatial Span subtests from the Wechsler Intelligence Scale for Children (WISC).

b. The protocol now indicates that for eligible participants, we will use information from the initial telephone screener (e.g. medical history, basic demographic information, etc) as study data. Subjects previously answered these questions a second time upon study entry.

6. Telephone screeners for potential participants were modified in the following ways:
   a. The control and proband participant screeners were updated to include questions that facilitate contact and scheduling (email address, preferred method of contact) and assist in the determination of whether a potential subject is likely to meet diagnostic criteria for an Autism Spectrum Disorder. The ordering of questions also has been changed to improve efficiency in gathering information (e.g., asking about exclusionary factors at the start of the interview).
   b. Consisent with these changes we have removed the line in the recruitment methods section stating, “No private identifiable information will be recorded without consent.”
7. New recruitment documents were developed for the Autism Speaks website, school administrators and for local service providers and community organizations.

Modification – Approved 01/11/2013 -

1. Our recruitment flyers were reformatted and updated with new images.
2. The Differential Ability Scale-Second Edition (DAS) will now be used with children who have difficulty completing the Wechsler tests (WPPSI or WASI).

Modification – Approved 05/13/2013 -

1. The Control Assent for children ages 5-12 years was mistakenly uploaded as the ASD Assent for children ages 5-12 years. The correct form was then uploaded and approved.
2. The protocol was amended in the following ways:
   a. The minimum age for healthy control children was lowered to 5 years to match the age range for ASD participants. Previously, the minimum age written in the protocol was mistakenly identified as 8 years for healthy controls.
   b. We previously administered social stories to all participants, but found that most participants including children understood study procedures without the support of these stories. We now present social stories to potential participants during the consent/assent process only when they show difficulty understanding the verbal explanation of the study, its procedures and the accompanying risks.

c. As an alternative option to mailing a copy of the Social Communication Questionnaire (SCQ) to potential probands, we now offer families the option of receiving them through secure email.
d. We now exclude biological parents of individuals with ASD only if they have a *major* psychiatric disorder, including but not limited to Bipolar Disorder, Schizophrenia, or any Axis II psychiatric condition. Previously we excluded parents with any psychiatric disorder, including depression or anxiety disorders which are common in this population.
e. We previously included proband subjects only if they had a 2nd grade reading level. We now include proband subjects if they have a 2nd grade reading level OR a level commensurate with their age and developmental status.
f. We now indicate that individual item scores are not double entered for all study tests.
g. We previously indicated in the study protocol that parents were required to be less than age 55 years. We now included parents age 55 or under.

Modification – Approved 05/13/2013 -

1. Dr. Suman Mohanty and Ms. Savanna Sablich have been added to the protocol as study personnel.

Subject recruitment: We have actively recruited family trios consisting of probands with ASD and each of their biological parents, and independent samples of healthy controls matched to the proband and parent groups on age and nonverbal IQ. We aimed to recruit 10 family trios during Year 1 (we enrolled 11 during Year 1) and 20 family trios per year during Years 2 and 3. We enrolled 19 family trios during the past year, so that we now have studied 30 family trios during the entire study period (target = 30). We aimed to recruit 8 healthy controls during Year 1 (we enrolled 7 controls during Year 1) and 32 controls per year during Years 2 and 3. We enrolled 39 healthy controls during the past year, so that we now have studied 46 controls over the entire study period (target through Year 2 = 40). Each of these individuals has completed oculomotor, manual motor, psychological and neuropsychological testing. We are on pace to meet our overall recruitment goals for both family trios and healthy controls. Our goal moving forward is to assess 5 family trios and 7-8 IQ- and age- matched healthy controls per quarter over the last year of the award.

Data quality assurance: The PI and Dr. Mosconi have completed quality assurance testing to ensure the integrity of sensorimotor and neurocognitive task administration and scoring. Dr. Mosconi has regularly observed neuropsychological test administrations performed by trained staff, as well as oculomotor and manual motor testing. Drs. Sweeney and Mosconi also have led weekly meetings with trained staff to ensure the quality of test administration and data analysis. Dr. Sweeney has overseen the scoring and analysis of eye movement data, and Dr. Mosconi has done the same

with the manual motor testing. Dr. Mosconi is scheduled to visit our consultant, Dr. Vaillancourt at the University of Florida in November to discuss preliminary findings. All clinical data collected up to this point has been entered into research databases. We have begun preliminary analyses of our data and aim to continue analyses over the course of the upcoming year. Manuscripts will be prepared shortly after the completion of the award.

III. KEY RESEARCH ACCOMPLISHMENTS

- We have continued subject recruitment and met all enrollment targets for the first two years of the study
- We have completed preliminary data analysis on subjects with ASD performing oculomotor and manual motor tasks and presented results at multiple scientific meetings (see below)

IV: REPORTABLE OUTCOMES

Peer Reviewed Manuscripts: No manuscripts based on data from this study have been published during the past year

Peer-reviewed Academic Presentations:

1. Mosconi MW, Vaillancourt DE, Mohanty S, Schmitt L, Greene RK, Sweeney JA. Sensorimotor abnormalities and their relationship to core social-communication features in autism spectrum disorder (ASD). Society for Neuroscience (SfN), (2013, November). San Diego, CA.
2. Schmitt LM, Mosconi MW, Sweeney JA. Eye movement abnormalities in autism spectrum disorder implicate sensorimotor and cognitive control brain systems. Society for Neuroscience (SfN), (2013, November), San Diego, CA.
3. Mohanty S, Vaillancourt DE, Coombes SP, Schmitt LM, Sweeney JA, Mosconi MW. Atypical brain functions underlying sensorimotor impairments in autism spectrum disorder. Society for Neuroscience (SfN), (2013, November), San Diego, CA.
4. Greene RK, Mosconi MW, Ragozzino ME, Schmitt L, Cook EH, Sweeney JA. Inhibitory control deficits in Autism Spectrum Disorders (ASD). Texas Autism Research Conference (TARRC), (2013, July). San Marcos, TX.
5. Schmitt LM, Mosconi MW, Cook EH, Sweeney JA. Decreased control of eye movement accuracy in individuals with autism spectrum disorder. Texas Autism Research Conference, (2013, July), San Marcos, TX.
6. Mosconi MW, Ragozzino ME, Schmitt LM, Cook EH, & Sweeney JA. Neurocognitive deficits underlying insistence on sameness in autism spectrum disorders. International Meeting for Autism Research (IMFAR), (2013, May). San Sebastian, SPAIN.
7. Mosconi MW, Ragozzino ME, Schmitt L, Cook EH, & Sweeney JA. Inhibitory control deficits in Autism Spectrum Disorders (ASD). American College of Neuropsychopharmacology (ACNP), (2012, December). Hollywood, FL.

V. CONCLUSIONS

During the first two years of this award, we have successfully maintained a pace of research progress that is consistent with that laid out in our original Statement of Work. We have developed strong staffing and data processing infrastructures as well as a program of referral services that has allowed us to recruit and examine 30 family trios and 46 healthy controls to date. We are on pace to complete recruitment during Year 3 and begin analyses of proband and family data during the upcoming last year of the award. We have maintained active collaborations with the consultants on this award, Drs. Daniel Corcos and David Vaillancourt, each of whom has worked directly with the study team over the past two years to develop manual motor tests and help ensure the quality of this data. During the upcoming year, they each will be heavily involved with our study team assisting in data analysis and interpretation.

Initial results from the proband studies are promising. We have found significant motor control deficits in subjects with ASD during manual motor tasks and oculomotor tasks. As the manual motor tasks used in this study had not previously been studied with subjects with ASD or their unaffected family members, this is encouraging new data that will strongly propel the present study efforts forward as we examine how these motor abnormalities run in families with ASD.

VI. REFERENCES

N/A

VII. APPENDICES

N/A

VIII. SUPPORTING DATA

N/A